

Appendicitis Prevention Device (APD)

Ananya Kachru

WHAT IS APPENDICITIS?

- ❖ Inflammation through pus
 - Followed by much pain
- ❖ Tends to occur when the appendix is blocked
 - Blockage by stool, an infection, foreign bacteria presence, or even cancer

Appendicitis



[Appendicitis Picture](#)

Note: Increase of neutrophils during appendicitis

IS THE APPENDIX IMPORTANT?



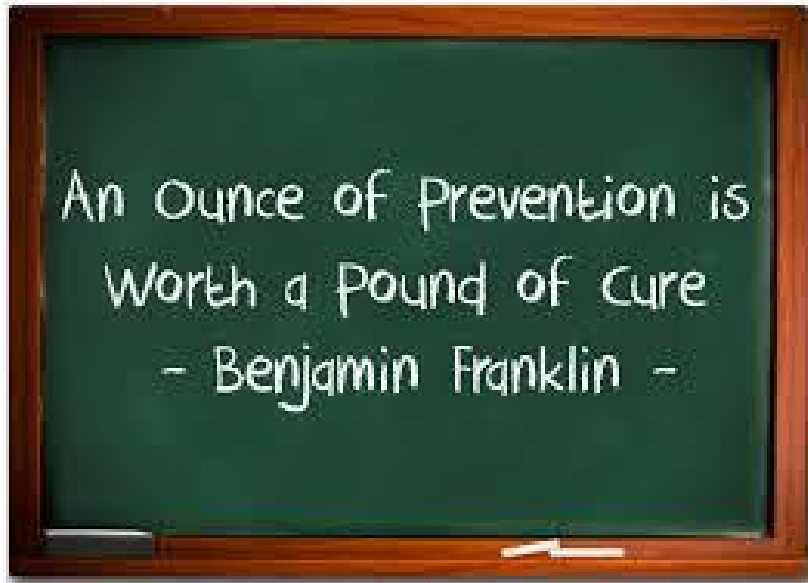
DUKE UNIVERSITY
MEDICAL CENTER

- ❖ Considered to be vestigial and unimportant
 - recent studies show that there is a particular significance to the appendix
- ❖ Currently, researchers have found that the appendix essentially acts as a ‘safe house’ for unharmed bacteria.
 - For example, when an individual suffers from dysentery or cholera, the appendix can activate as a ‘reboot mechanism’ for the digestive system.

DUMC found the purpose

PURPOSE

- ❖ As one in every fifteen people suffer from appendicitis, it is important to design a preventive measure to preserve the appendix!



IMPORTANCE



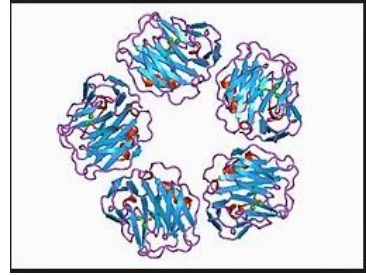
- ❖ Crucial because no functioning preventive measure for appendicitis
- ❖ Anyone who suffers from appendicitis must undergo appendectomy or receive antibiotic therapy
 - Appendectomy is a common procedure, but complications are evidently plausible and it is a significant inconvenience.
 - On the other hand, antibiotic therapy is once again not very effective and causes much pain within individual patients.

IMPORTANCE OF PREVENTIVE MEASURE



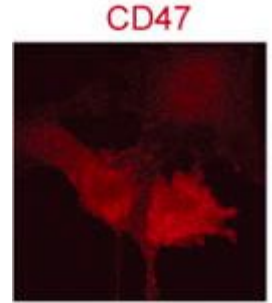
- ❖ Ease and more comfort for general population
- ❖ Cost-effectiveness and quality (complications etc.)
- ❖ Appendectomy and antibiotic therapy will no longer have to be as prevalent in the health industry
 - financial burden will be lifted from potential patients

HOW WILL THE APD ADDRESS THE CURRENT PROBLEM?



CRPs

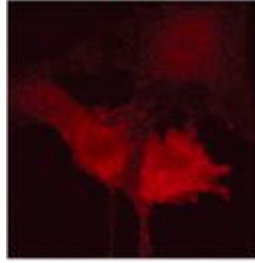
- ❖ Reengineer Bacteroides (most abundant in the appendix)
- ❖ C-Reactive Proteins (CRPs)
 - Typically a marker of inflammation in the cardiovascular system
 - APD will utilize the gene that encodes for this protein
 - express CRPs at the site of inflammation in the appendix
- ❖ CRPs prevalent → signal molecule will bind to receptor for the production of Cluster of Differentiation 47 proteins (CD47)
 - CD47 leads to de-inflammation of the appendix
 - inhibition of activation and induced apoptosis of neutrophils



LOOP... INFLAME AND DE-INFLAME

- ❖ Inflammation → CRPs
- ❖ CRPs → CD47
- ❖ CD47 → Inhibition of neutrophil activation and induced apoptosis
- ❖ Reduced neutrophils → De-inflammation

CD47



NEUTROPHIL

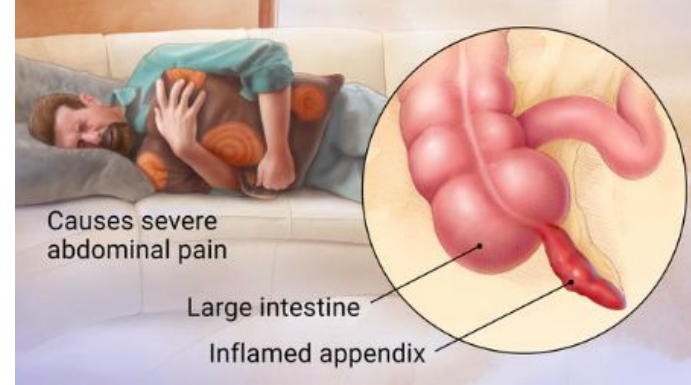


COMPETING TECHNOLOGIES

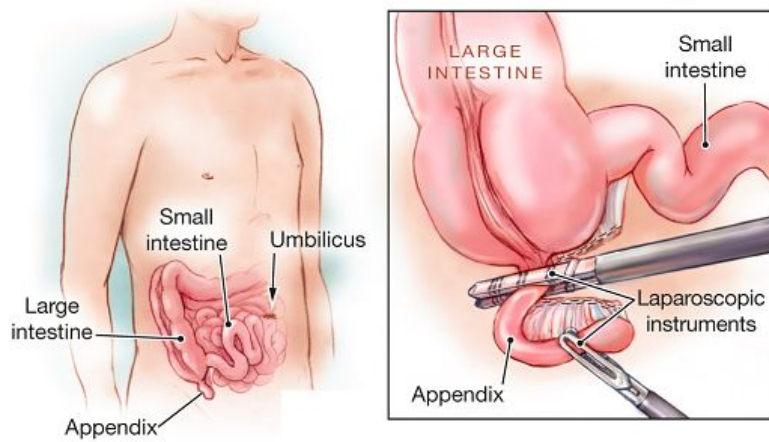
Currently: appendicitis is dealt with through two methods

- ❖ Primarily an appendectomy procedure
- ❖ Recently even an antibiotic therapy
 - especially with patients enduring uncomplicated acute appendicitis

Note: No preventive measure being used at this point



APPENDECTOMY



- ❖ Emergency surgical operation
 - Appendectomy is the most common treatment for appendicitis
- ❖ Utilizes laparoscopic instruments to remove the appendix
 - Incision in the right abdomen allows for proper removal of the appendix

An individual undergoing the procedure would lose their 'safe house' of bacteria.

This can be deemed as not beneficial in many situations.

ANTIBIOTIC THERAPY

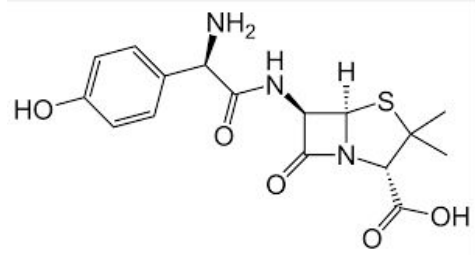


Extremely controversial, this non-operative treatment has recently shown promise in cases of uncomplicated, acute appendicitis.

This antibiotic therapy is impactful as it essentially can de-inflate the appendix after symptoms are shown.

There have been two approaches to antibiotic therapy so far...

FIRST APPROACH... THE NOTA STUDY (NONOPERATIVE TREATMENT FOR ACUTE APPENDICITIS)



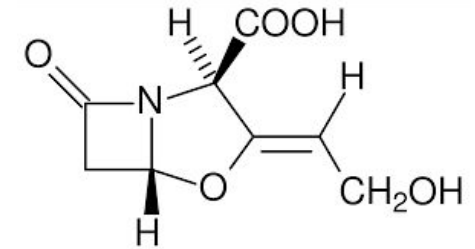
Amoxicillin

❖ Amoxicillin and clavulanic acid to de-inflate the appendix and avoid operation

➤ found that antibiotics were safe and effective in reducing operation rate, complications, as well as overall cost

❖ Recurrences of abdominal pain for patients was less than 14%

➤ pain could still be efficiently treated with further intake of antibiotics

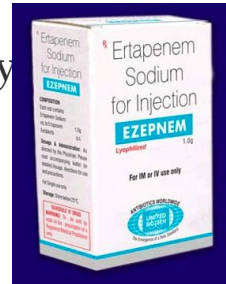


Clavulanic Acid

SECOND APPROACH...ANTIBIOTIC THERAPY VS APPENDECTOMY FOR TREATMENT OF UNCOMPLICATED ACUTE APPENDICITIS

- ❖ Intravenous ertapenem, oral levofloxacin, and metronidazole
- ❖ Effective criterion
 - patients being discharged from the hospital without the need for surgery as well as no repeat of appendicitis within a follow-up period (1 year)

Overall, researchers found that this antibiotic treatment marginally did not meet the criterion they had set at the beginning of the study



THINKING TIME!

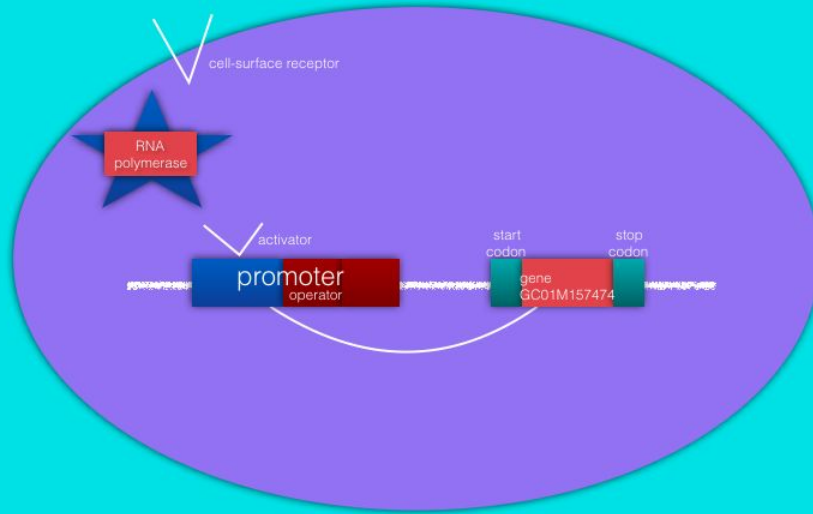


- ❖ Originally, I was hoping to be able to use amoxicillin and clavulanic acid in my APD.
 - Neither of these are naturally produced as proteins in the human body
 - Not possible to genetically modify a particular gene to secrete both amoxicillin and clavulanic acid
- ❖ Appendicitis is accompanied with an increase in neutrophils, white-blood cells which respond to infection.
 - Neutrophils=inflammation → inducing apoptosis may help to reduce inflammation
 - Researchers have found the CD47 signals neutrophil death (white blood cells)

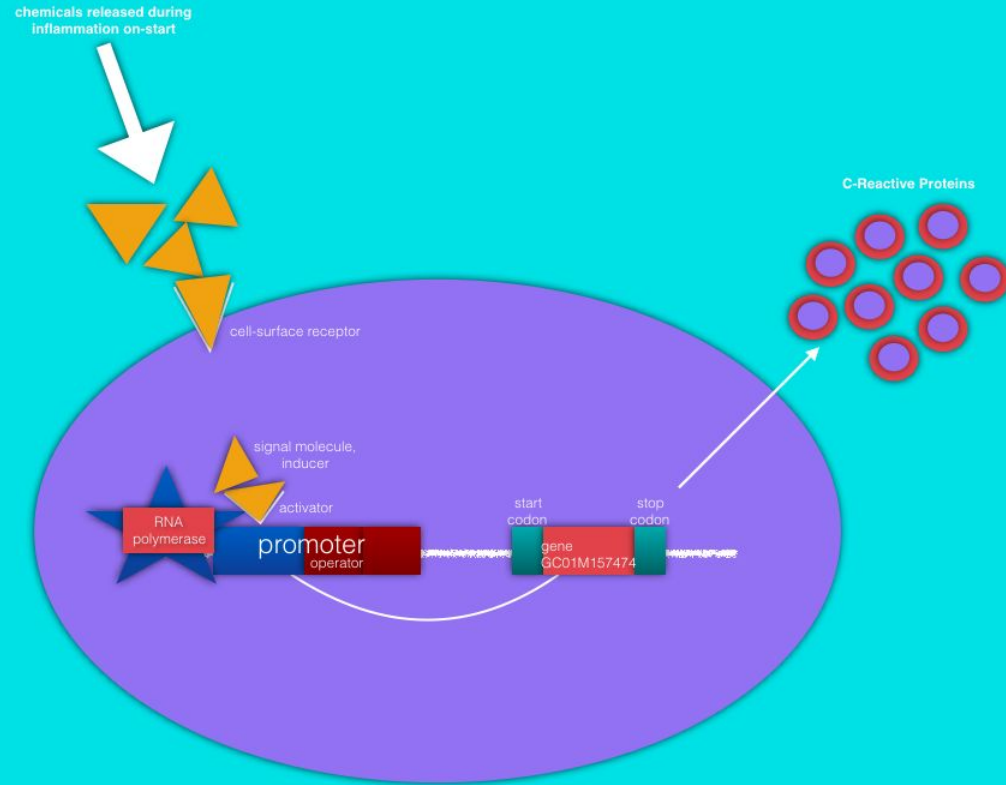
This inspired my design as it became a plausible de-inflammation technique.

DESIGN

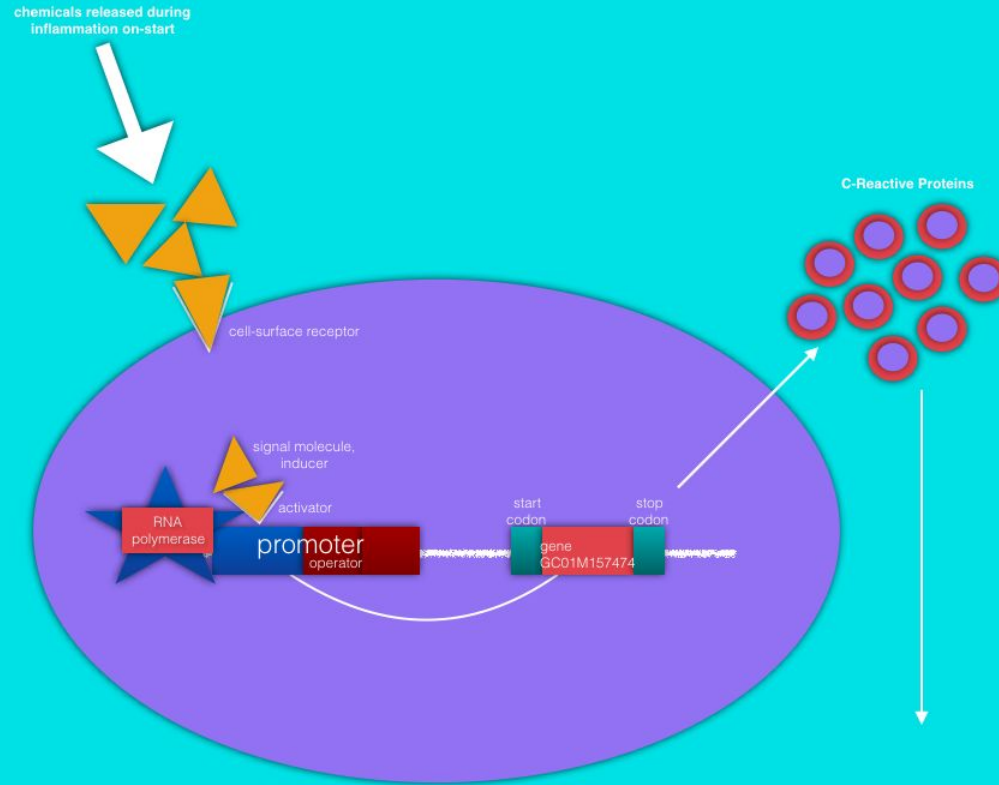
Genetic Pathway for C-Reactive Protein



Genetic Pathway for C-Reactive Protein

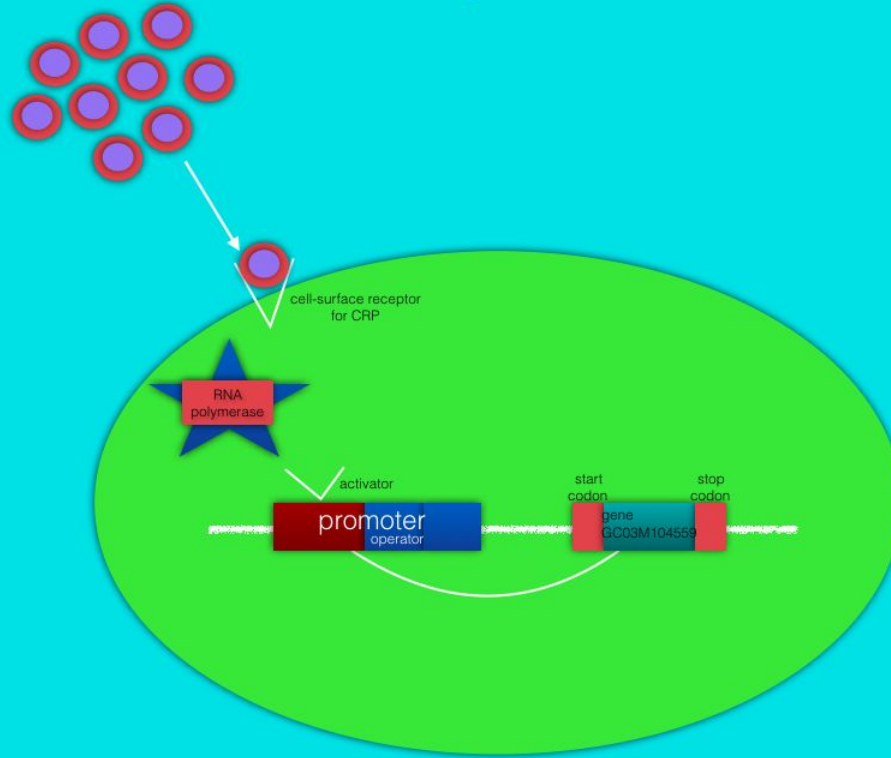


Genetic Pathway for C-Reactive Protein

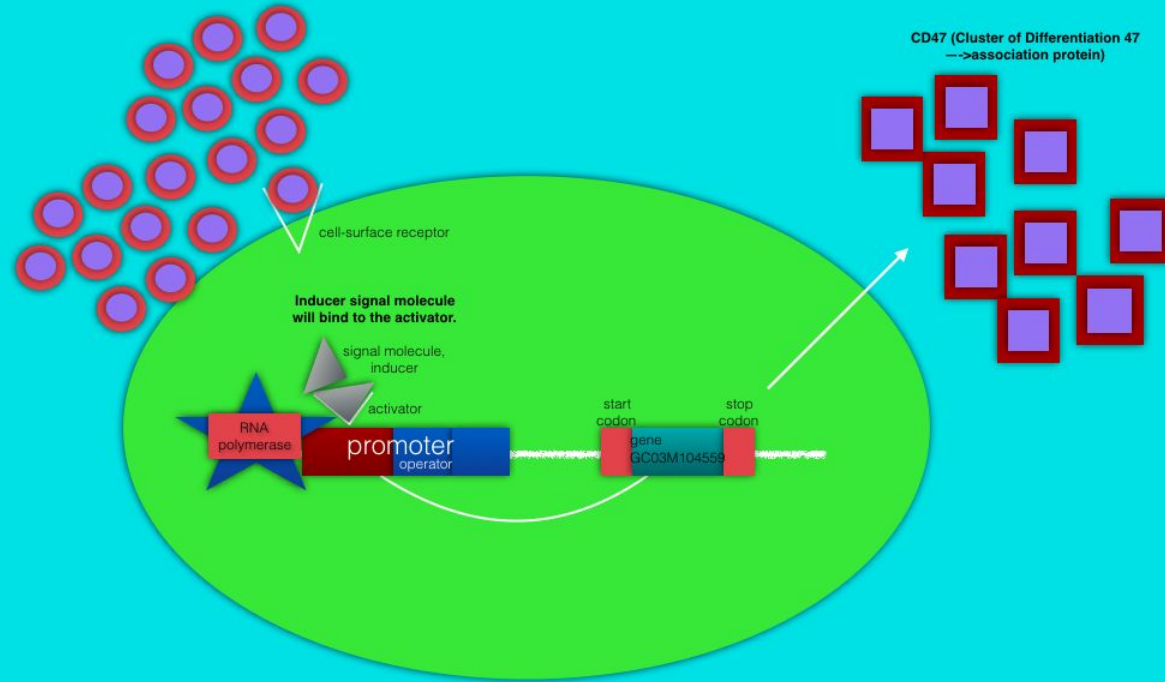


C-Reactive Proteins will regulate the autoinducers for the CD47 genetic pathway...

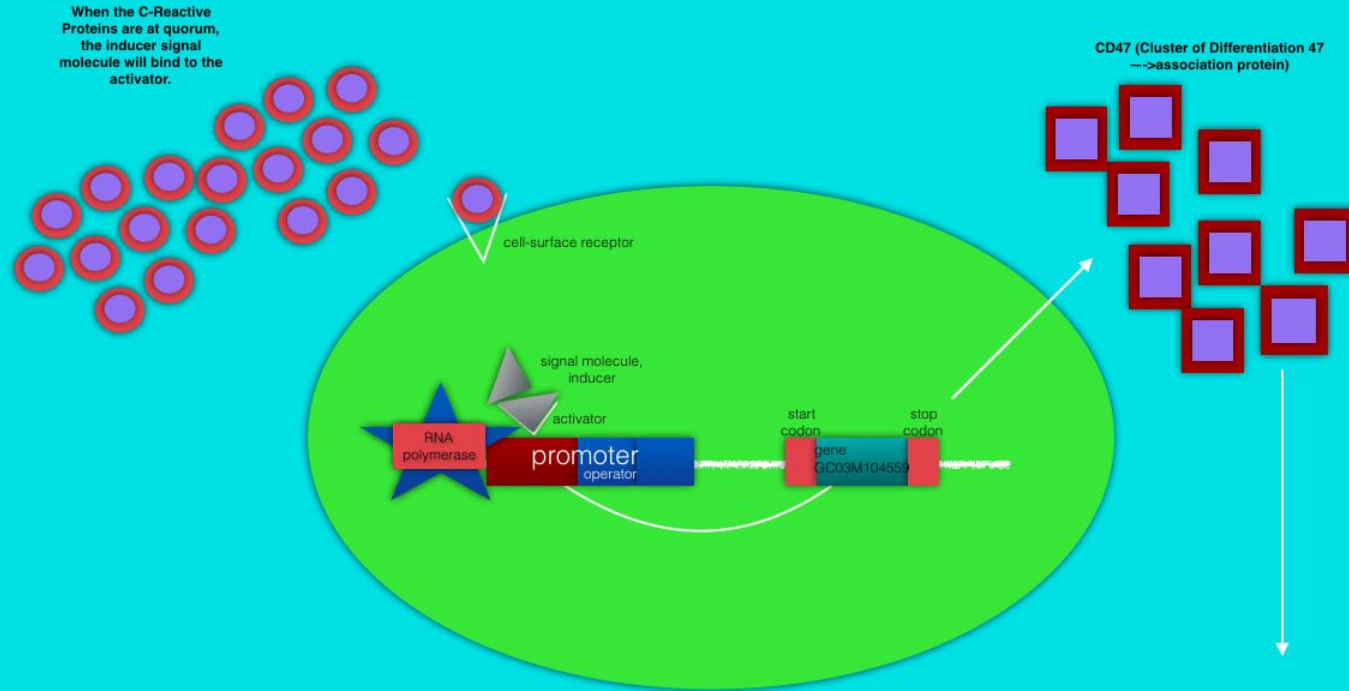
Genetic Pathway for CD47 Protein



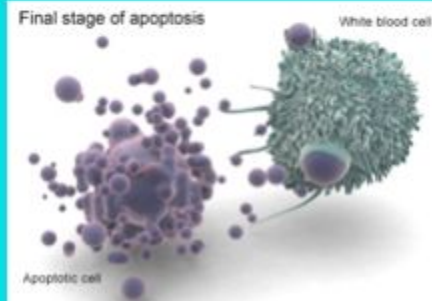
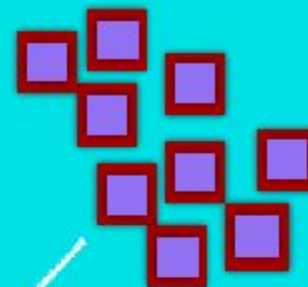
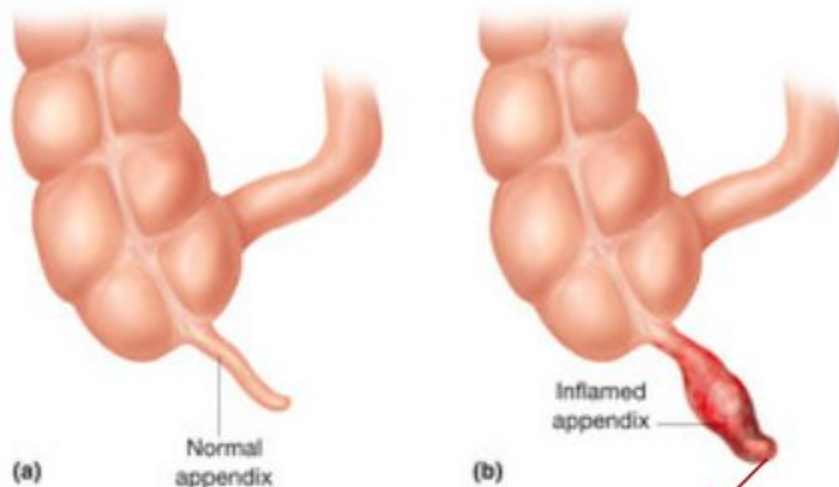
Genetic Pathway for CD47 Protein



Genetic Pathway for CD47 Protein



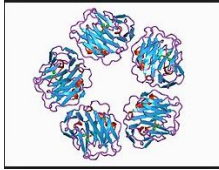
The CD47 protein can inhibit neutrophil activation, and essentially induce T-cell apoptosis. This will reduce inflammation in the appendix.



CD47 signals T-cell apoptosis...
Goodbye to your inflammation!

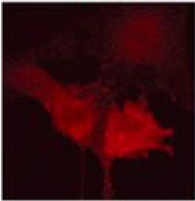
EXPECTED RESULTS

- 1) C-Reactive Proteins to be produced at the onset of inflammation.
- 2) C-Reactive Proteins are apparent → Cluster of Differentiation 47 produced
- 3) CD47 will inhibit neutrophil activation and eventually cause apoptosis
- 4) Apoptosis and reduction of neutrophils in the appendix result in de-inflammation

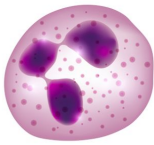


CRPs

CD47



NEUTROPHIL



Successful solution: Loop of inflammation and de-inflammation

Thereby, appendicitis will be an eliminated ailment...

EXPECTATIONS CONT...

Truth Table

Presence of Inflammation	Presence of CRP (C-Reactive Proteins)	Presence of CD47 (Cluster of Differentiation 47)	Neutrophil inhibition and apoptosis	De-inflammation
0	0	0	0	0
1	1	1	1	1

ADVANTAGES

- ❖ No other preventive measure for appendicitis (currently)
- ❖ 'Solutions' to inflammation in the appendix are appendectomy or antibiotic therapy
 - appendectomy removes an organ that is a 'safe house' for harmless bacteria
 - antibiotic therapy requires tremendous pain before the antibiotics are effective.



WORTH FUNDING?

YES!



- ❖ Only appendicitis prevention device
- ❖ Less painful and troublesome than appendectomy as well as antibiotic therapy

Of course a lot of clinical research and funding would be necessary to develop the APD successfully, but it is promising because it is cost effective and requires much less medical intervention at the onset of intervention in the appendix.

POTENTIAL PROBLEMS



- ❖ Procedure for inserting the bacteria would have to be developed much farther
- ❖ Bacteroides survives in the appendix, but it is unknown if it will survive with the two additional genes.
 - As the bacteria's genotype is being altered, ensuring that the redesigned Bacteroides can survive in the appendix is very important to the design.
- ❖ CD47 binding to the neutrophils could potentially destruct too many neutrophils
 - These are neutrophils necessary (immune system), but in excess they contribute to unnecessary inflammation.

SELECTION OF FREQUENTLY ASKED QUESTIONS (MORE ON WIKI)

How would you ensure safety?

- ❖ If regular safety precaution is taken, the employees working on the development of this design will be adequately taken care of!

In what ways could the evolution of cells you've engineered negatively affect use of your design in the future? Mutations...

- ❖ CRP gene may not react as expected
- ❖ CD47 gene is already prevalent in the appendix, but its signal molecule for the activator tends to not depend on the presence of a CRP binding a cell-surface receptor...
- ❖ Both alterations within Bacteroides could result in problems occurring in the future



FAQS CONTINUED

Are there any inefficiencies or shortcomings as proposed by existing technologies?

- ❖ Compared to Appendectomy: APD does not remove the appendix
 - Researchers → appendix is important as a safe house for harmless bacteria
 - Several groups of people still believe that it is vestigial.
 - *For those, removing the appendix at the onset of inflammation may seem helpful.*
- ❖ Compared to Antibiotic Therapy: No shortcomings

Does your design pose dangers to the environment, lab safety, and the security of the public?

- ❖ The design does not pose tangible risks to the environment.
- ❖ The design does not pose tangible risks to lab safety.
- ❖ Because of scrutinizing lab testing and regulation, the APD should not and would not pose danger to the security of the general public.



WORTH THE RISKS?

There will always be some risk associated with scientific progress, but the potential rewards that the APD offers truly do outweigh any plausible risks.

- ❖ APD would prevent appendicitis
 - USA: 200,000 ppl/year undergo appendectomy
 - Millions of people worldwide would be saved from the pain or trauma that accompanies current practices
- ❖ Both the treatments for appendicitis today- appendectomy and antibiotic therapy- are costly.
 - Once the APD is synthesized, its cost will be very minimal and it will be much more effective in totality



TESTING



- 1) Prototype with the CRP gene and the CRP receptor, which initiates CD47 production
- 2) Simulate what occurs in the appendix during the onset of inflammation in a petri dish
- 3) Inflammation chemicals → binding of signal molecule to activator
- 4) Transcribe, translate, and synthesize proteins
- 5) CD47 association proteins should bind to the neutrophils
 - a) Inhibit activation or induce apoptosis, if not both processes consecutively

De-inflammation through reduction of neutrophils in the appendix signals a working and an effective device

BENEFITS OF TESTING



Improvements: Show if there are particular gaps that prevent the system from properly functioning

Reveal Greater Potential:

- ❖ Variations in results could find if altering more or less of the bacteria's genotype may positively help the APD
- ❖ Greater potential could also root from an unexpected result at the end of the procedure, one which may be helpful to the APD's overall design.

Works Cited

- "Appendicitis Symptoms, Causes, Surgery, and Recovery." *WebMD*. WebMD. Web. 04 Aug. 2016.
- "Appendicitis Therapy." *Womens Best*. Web. 04 Aug. 2016.
- "Appendicitis." *Wikipedia*. Wikimedia Foundation. Web. 04 Aug. 2016.
- "Cluster of Differentiation 47 Gene." *Gene Cards*. Web. 04 Aug. 2016.
- "C-reactive Protein." *C-reactive Protein: MedlinePlus Medical Encyclopedia*. Web. 04 Aug. 2016.
- "C-Reactive Protein Gene." *Gene Cards*. Web. 04 Aug. 2016.
- "Early Appendicitis Symptoms, Signs, Pain, Test, & Surgery." *MedicineNet*. Web. 04 Aug. 2016.
- "Genes and Mapped Phenotypes." *National Center for Biotechnology Information*. U.S. National Library of Medicine. Web. 04 Aug. 2016.
- "Genes and Mapped Phenotypes." *National Center for Biotechnology Information*. U.S. National Library of Medicine. Web. 04 Aug. 2016.
- Leigh, D. A., K. Simmons, and E. Norman. "Bacterial Flora of the Appendix Fossa in Appendicitis and Postoperative Wound Infection." *Journal of Clinical Pathology* 27.12 (1974): 997-1000. Web.
- "Mechanisms of CD47-induced Caspase-independent Cell Death in Normal and Leukemic Cells: Link between Phosphatidylserine Exposure and Cytoskeleton Organization." *Home*. Web. 03 Aug. 2016.
- "Result Filters." *National Center for Biotechnology Information*. U.S. National Library of Medicine. Web. 02 Aug. 2016.
- "Result Filters." *National Center for Biotechnology Information*. U.S. National Library of Medicine. Web. 03 Aug. 2016.
- "Result Filters." *National Center for Biotechnology Information*. U.S. National Library of Medicine. Web. 03 Aug. 2016.
- "Result Filters." *National Center for Biotechnology Information*. U.S. National Library of Medicine. Web. 04 Aug. 2016.